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REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-30 are pending. Non-elected claims 16-22 were withdrawn from consideration by the Examiner. Applicants request rejoinder of the withdrawn method claims upon an indication that a product claim is allowable.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The limitations "specific" and the phrase beginning "with the proviso" are deleted because they are not required for patentability. Similarly, the typographical error "episteric" is deleted because it is not required for patentability.

Double Patenting

Claims 1-15 were rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-8 of Patent No. 6,277,627. Applicants traverse.

Claims 1-8 of Patent No. 6,277,627 are directed to biosensors comprising a glucose binding protein and a reporter group. As admitted by the Examiner on page 8 of the Action, "The *disclosure* of [Patent No. 6,277,627] differs from the instant in that [it does not] specifically exemplify any other bPBP other than GBP" (emphasis added). As explained below, the only other bacterial periplasmic binding proteins mentioned in the *specification* of Patent No. 6,277,627 are MBP and PBP, which are discussed in the context of attaching reporter groups at "nonallosteric (peristeric) reporter sites" in Example 2. The *claims* of Patent No. 6,277,627 are limited to glucose binding proteins. No other types of bacterial periplasmic protein are recited in claims 1-8.

In contrast, the instant claims 1-14 are directed to biosensors comprising a bacterial periplasmic binding protein other than glucose binding protein and maltose binding protein and at least one reporter group. In the presently claimed invention, the amino acid positions where the reporter groups are attached are allosteric or endosteric sites. There is no teaching or suggestion in claims 1-8 of Patent No. 6,277,627 that other types of bacterial periplasmic binding protein could be used to make the presently claimed biosensors. Therefore, it would not have been obvious from claims 1-8 of

Patent No. 6,277,627 to exclude glucose binding proteins and maltose binding proteins from the biosensors of present claims 1-14.

Furthermore, the instant claim 15 is directed to biosensors comprising a bacterial periplasmic binding protein and at least one reporter group attached at one or more amino acid positions which is an endosteric site (see page 20, lines 18-20, of the instant specification). Neither the specification nor the claims of Patent No. 6,277,627 teach or suggest attachment of a reporter group to the bacterial periplasmic binding protein at an endosteric site. Therefore, it would not have been obvious from claims 1-8 of Patent No. 6,277,627 to selectively use endosteric sites in the biosensors of present claim 15.

Withdrawal of the double patenting rejection is requested.

35 U.S.C. 112 – Definiteness

Claims 1-15 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The term "specific" is deleted from claims 1, 7-8 and 15 because this limitation is not required for patentability.

The term "position" refers to the amino acid sequence of the bPBP. U.S. Patent 6,277,627 is cited for describing *E. coli* periplasmic binding proteins, including the amino acid sequence of GBP, on page 2, lines 3-6, of Applicants' specification. Its contents are incorporated by reference on page 57, lines 11-14, of Applicants' specification. No recitation of GBP's amino acid sequence is necessary because numbering of the amino acid positions is well known in the art and would be clearly understood by the skilled artisan. For example, recitation of GBP's amino acid sequence was not required for the Examiner to thoroughly search the subject matter of the claims.

Claim 4 refers to the ligand of the biosensor (see claim 1). The wild-type bPBP binds its natural ligand (referred to as the "normal binding partner" on page 4 of the Action). But the ligand of the biosensor is not necessarily the natural ligand of the wild-type bPBP and does not necessarily bind to the wild-type bPBP. For example, Hellinga & Richards (J. Mol. Biol. 222:763-785, 1991) and Marvin & Hellinga (Proc. Natl. Acad.

Sci. USA 98:4955-4960, 2001) were cited on page 6 of Applicants' specification as demonstrating structure-based redesign of ligand-binding specificity. Using such redesign methods as taught in the prior art, Benson et al. (Biochemistry 41-3262-3269, 2001) replaced the maltose-binding pocket of MBP with an oxygen-binding pocket.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1 and 3-15 were rejected under Section 102(e) as allegedly anticipated by Amiss et al. (U.S. Patent Publication 2003/01344346). Applicants traverse because the reporting group is not permitted to be attached at position 149 of GBP in claim 1.

Claims 1 and 3-15 were rejected under Section 102(e) as allegedly anticipated by Amiss et al. (U.S. Patent 6,855,556). Applicants traverse because the reporting group is not permitted to be attached at position 149 of GBP in claim 1.

Withdrawal of the Section 102 rejections is requested because all limitations of the claimed invention are not disclosed by the cited documents.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). Rigorous application of this requirement is

the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-15 were rejected under Section 103(a) as allegedly unpatentable over Hellinga et al. (WO 99/34212). Applicants traverse.

On page 7 of the Action, it was alleged, "Hellinga et al. disclose that the strategy for introducing reporter groups into the exemplified GBP was successfully use with MBP and PBP" and, thus, the Examiner contended that "it would have been obvious to one of ordinary skill in the art at the time of the invention to apply the methods set forth by Hellinga et al. in making GBP based biosensors to the making of biosensors comprising other periplasmic binding proteins." Finally, he alleged, "One would have had a reasonable expectation of success as Hellinga et al. disclose the ability to apply strategies to multiple periplasmic binding proteins." Although no citations to the prior art are made in this portion of the Action, it appears that the Examiner is referring to pages 18-19 of WO 99/34212. Example 2 of WO 99/34212 is a description of nonallosteric (peristeric) sites where reporter groups are attached in GBP, and other work in MBP and PBP that also involves peristeric sites is discussed.

Applicants' claimed invention (see especially claims 1 and 15) is directed to biosensors in which at least one reporter group is attached at one or more amino acid positions of a bacterial periplasmic binding protein which are allosteric or endosteric sites (see pages 20-21 of the specification for a discussion of the distinguishing features of endosteric, peristeric, and allosteric sites). Moreover, the periplasmic binding protein is not a glucose binding protein or a maltose binding protein in claim 1. Biosensors of claims 1 and 15, which attach at least one reporter group to one or more amino acid positions of a bPBP which are allosteric or endosteric sites, exclude the peristeric site mutants of GBP, MBP and PBP.

WO 99/34212 does not teach or suggest attaching at least one reporter group to endosteric sites of a bPBP. And the only pPBP in which at least one reporter group is

attached at allosteric sites is glucose binding protein. Therefore, a reasonable expectation of success to make Applicants' presently claimed invention is lacking.

Claims 1-15 were rejected under Section 103(a) as allegedly unpatentable over Hellinga et al. (U.S. Patent 6,277,627). Applicants traverse.

On pages 8-9 of the Action, it was alleged, "Hellinga et al. disclose that the strategy for introducing reporter groups into the exemplified GBP was successfully use with MBP and PBP" and, thus, the Examiner contended that "it would have been obvious to one of ordinary skill in the art at the time of the invention to apply the methods set forth by Hellinga et al. in making GBP based biosensors to the making of biosensors comprising other periplasmic binding proteins." Finally, he alleged, "One would have had a reasonable expectation of success as Hellinga et al. disclose the ability to apply strategies to multiple periplasmic binding proteins." Although no citations to the prior art are made in this portion of the Action, it appears that the Examiner is referring to cols. 7-8 of U.S. Patent 6,277,627. Example 2 of U.S. Patent 6,277,627 is a description of nonallosteric (peristeric) sites where reporter groups are attached in GBP, and other work in MBP and PBP that also involves peristeric sites is discussed.

Applicants' claimed invention (see especially claims 1 and 15) is directed to biosensors in which at least one reporter group is attached at one or more amino acid positions of a bacterial periplasmic binding protein which are allosteric or endosteric sites (see pages 20-21 of the specification for a discussion of the distinguishing features of endosteric, peristeric, and allosteric sites). Moreover, the periplasmic binding protein is not a glucose binding protein or a maltose binding protein in claim 1. Biosensors of claims 1 and 15, which attach at least one reporter group to one or more amino acid positions of a bPBP which are allosteric or endosteric sites, exclude the peristeric site mutants of GBP, MBP and PBP.

U.S. Patent 6,277,627 does not teach or suggest attaching at least one reporter group to endosteric sites of a bPBP. And the only pPBP in which at least one reporter group is attached at allosteric sites is glucose binding protein. Therefore, a reasonable expectation of success to make Applicants' presently claimed invention is lacking.

Withdrawal of the Section 103 rejections is requested because the invention as claimed would not have been obvious to one of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending objections and rejections contained in this Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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